AMENDMENTS TO THE DRAWINGS

The attached two Replacement Sheets include changes to Figures 5D (2) and 5D (3). These Replacement Sheets replace original sheets 12 and 13 containing Figures D (2) and D (3). The numbering of these figures has been amended as follows:

original Figure D (2) (sheet 12) is numbered as Replacement Sheet Figure 5D (2); and

original Figure D (3) (sheet 13) is numbered as Replacement Sheet Figure 5D (3).

REMARKS

Claim amendments

Applicants have amended claims 1, 2, and 9. Claims 3-8, 12, and 13 were cancelled by earlier amendment. Claims 1, 2, and 9-11 are pending.

The claims 1 and 2 have been amended to more distinctly claim subject matter. These amendments are supported by at least pages 6, 16, and 17 of the application as filed. Claim 9 has been amended to remove reference to non-elected subject matter. These amendments do not add new matter and their entry is respectfully requested.

Withdrawal of claim 11

The Examiner withdrew claim 11 from consideration. The Examiner alleges that, as amended in the last Response, claim 11 is directed to an invention that is independent or distinct from the invention originally claimed. Office Action at 2. Specifically, the Examiner alleges that a method of treating tumors with a MUC1 molecule (claim 11) and a method of production or identification of a MUC1 molecule (claims 1 and 2) are distinct because they comprise different steps and use different products and would supposedly require different searches, which the Examiner considers a serious burden. *Id.* Applicants traverse.

The M.P.E.P. instructs that restriction between patentably distinct inventions is proper when the inventions are independent and distinct as claimed *and* that there would be a *serious* burden on the examiner if restriction were not required. M.P.E.P. § 803(I). Applicants submit that examining claim 11 with claims 1, 2, and 9 would not impose the *serious* burden necessary to support restriction between these claims.

As an initial matter, this Examiner grouped claim 11 with claims 1-3, 7, 9, and 10 (see Restriction Requirement mailed February 4, 2008) and, following Applicants' election of this restriction group, acknowledged that it was under examination (see Office Action mailed October 28, 2008 at 2). In fact, in the last Office Action, the Examiner rejected claim 11 under 35 U.S.C. §§ 101, 112, first paragraph, and 112, second paragraph. In response, and at the Examiner's request, Applicants amended claim 11 by merely removing the references to unelected subject matter and amending the claim to conform to US practice (rewriting the "use" claim as a "method" claim). These amendments made no substantial change to the claimed subject matter that should lead the Examiner to deviate from this initial assessment that claim 11 is properly grouped with claims 1, 2, and 9.

Moreover, claims 1 and 2 recite methods of producing or identifying a MUC1 molecule, while claim 11 recites a method of using a MUC1 molecule obtainable by the methods of claims 1 or 2 to treat cancer. Accordingly, a search on the methods of claims 1 and 2 will also identify the references most relevant to the patentability of the method of claim 11 and thus would not impose a serious search burden. Accordingly, Applicants respectfully request that claim 11 be examined with claims 1, 2, 9, and 10 in this application.

Priority

With this Response, Applicants are filing an Application Data Sheet that indicates the filing date of European Patent Application No. 02016440.6.

Amendments to the drawings

The Examiner objected to drawings for minor informalities. As requested by the Examiner, Applicants have amended the numbering of Figures D (2) and D (3) on drawing sheets 12 and 13 to insert the number "5" in the accompanying two (2) "Replacement Sheets" of drawings, rendering the objection moot. These amendments do not add new matter.

Objections to the claims

The objection to claim 9 for reciting non-elected inventions is rendered moot by Applicants' amendment of the claim. The objection to claims 1, 2, 9, and 10 for reciting "wherein the mixture of MUC1 molecules is a cell line that expresses and/or secretes tumor associated MUC1 molecules" is rendered moot by Applicants' amendment of claims 1 and 2.

Rejections under 35 U.S.C. § 103(a)

The previous rejection of claims 1, 2, and 9-11 under 35 U.S.C. § 103(a) was withdrawn. Claims 1, 2, 9, and 10 are newly rejected under 35 U.S.C § 103(a) as allegedly unpatentable over Snijdewint *et al. Cancer Immunol. Immunother.* 48:47-55 (1999) (*Snijdewint*), in view of Ryuko *et al. Tumor Biol.* 21:197-210 (2000) (*Ryuko*), Torabi-Pour *et al. Biomed Chromatogr.* 15:18-24 (2001) (*Torabi-Pour*), U.S. Patent No. 4,939,240 by Chu *et al.* (*Chu*), and U.S. Patent No. 7,402,403 to Robertson *et al.* (*Robertson*). The Examiner alleges that *Snijdewint* reports isolating a MUC1 preparation from the supernatant of the breast cancer cell line ZR-75-1 by affinity binding to the MUC1 antibody 139H2 and that these preparations had no effect on

PBMCs from healthy women and a stimulating effect on PBMCs from three of twelve ovarian cancer patients. Office Action at 7.

The Examiner acknowledges that *Snijdewint* does not disclose 1) isolating MUC1 from a cell lysate, 2) that the 139H2 antibody has the properties recited in the claims, or 3) formulating the MUC1 molecule in pharmaceutically or diagnostically acceptable form and relies on *Ryuko, Torabi-Pour, Chu,* and *Robertson* to remedy these defects. Office Action at 8. In particular, *Ryuko* is cited to allegedly demonstrate that the 139H2 antibody binds the same MUC1 epitope and has similar reactivity patterns as the A76-A/C7 antibody. The Examiner concludes that it would have been obvious to substitute one known antibody for another equivalent antibody and that isolating a tumor antigen from a cell lysate and methods of formulating a tumor antigen in pharmaceutical or diagnostic form were well known in the art as evidenced by *Torabi-Pour, Chu,* and *Robertson*, respectively. Office Action at 10. In response to Applicants' arguments that *Snijdewint* does not teach or suggest methods of producing MUC1 molecules that can generate an immune response in humans, the Examiner alleges that "Snijdewint et al. disclose that significant PBMC proliferation can be induced in more than 50% of the ovarian cancer patients by the 20 mer and/or 60 mer MUC1 tandem repeat peptide [sic], which confirms the presence of MUC1-antigen-specific T cells in the blood of ovarian cancer patients" and contends that that this effect is "an immune response." *Id.* at 11. Applicants traverse.

The M.P.E.P. instructs that rejections under 35 U.S.C. § 103(a) must consider the invention as a whole, and not merely be based on the differences between the cited reference and the claims. *See* M.P.E.P. § 2141.02(I). Distilling an invention down to a

gist or thrust disregards this requirement. *Id.* at 2141.02(II). Applicants respectfully submit that the Examiner's rejection disregards the directive to view the invention as a whole, since it appears to be based on the allegation that *Snijdewint* reports isolating MUC1 from the supernatant of a cancer cell line with an antibody that shares some characteristics with the A76-A/C7 antibody (as allegedly evidenced by *Ryuko*). Applicants aver that the Examiner has not fully considered the pending claims or the teachings of the cited references, particularly *Snijdewint* and *Ryuko*. In particular, Applicants submit that:

1) *Snijdewint* does not teach or suggest methods of producing or identifying MUC1 molecules capable of generating an immune response in humans,

2) the antibody used in the methods of *Snijdewint* does not have the features recited in the claims, as evidenced by *Ryuko*, and

3) the remaining references, either alone or in combination, do not remedy the defects of *Snijdewint* and *Ryuko.*

Snijdewint does not teach or suggest methods of producing or identifying MUC1 molecules capable of generating an immune response in humans

Snijdewint does not teach or suggest methods of producing or isolating MUC1 molecules which are *able to generate an immune response in humans* and are expressed or secreted by a cell or obtained from its lysate. The Examiner appears to equate *in vitro* proliferation of PBMCs incubated with an antigen (either synthetic MUC1 peptides or MUC1 isolated from a culture supernatant by the 139H2 antibody) with generating an immune response to the antigen in humans. However, at best, these PBMC proliferation assays merely reveal *pre-existing* "MUC-1-antigen-specific T cells in the blood of [some] ovarian cancer patients...." *Snijdewint* at 51, right column, first full

paragraph. Thus, the proliferation of PBMCs only serves as a diagnostic test for *existing* MUC1-reactive T cells and does not teach or suggest that an immune response was (or could be) generated by the MUC1 isolated by *Snijdewint's* methods.

In fact, the MUC1 molecules isolated by *Snijdewint's* methods would not be expected to *generate* an immune response in view of *Snijdewint's* teaching that PBMCs isolated from healthy donors (which would not be expected to contain pre-existing MUC1-antigen-specific T cells) did not proliferate in response to this MUC1. *See Snijdewint* at 49 "Effect of MUC1 on PBMC proliferation." The weak effect of MUC1 on proliferation of PBMCs from only three out of twelve cancer patients—where some pre-existing MUC1-antigen-specific T cells might be expected—led the authors to conclude that "[t]he weak proliferative responses we found made it *impossible* to find positive or negative correlations [of humoral responses to MUC1 with cellular responses to MUC1 and its tandem repeats]." *Snijdewint* at 53, left column, second full paragraph (emphasis added). *Snijdewint* further teaches that MUC1 co-incubated with *C. albicans* extract had an *immunosupressive* effect on PBMCs from almost all of the nine ovarian cancer patients tested. *Snijdewint* at 49, right column "Effect of MUC1 on proliferation of *C. albicans*-stimulated PBMCs." This immunosuppressive effect of MUC1 was also known in the art. *See Snijdewint* at 48, left column, first full paragraph; *see also* reference "2" in *Snijdewint* by Agrawal *et al.* (entitled "Cancer associated MUC1 mucin inhibits human T-cell proliferation, which is reversible by IL-2"). Thus, the skilled artisan considering *Snijdewint* would not consider it as a basis for methods to produce or isolate MUC1 molecules able to generate an immune response in humans. *Snijdewint's* reports stand in contrast to the examples in the application, which show that MUC1

produced according to the methods of the invention is both immunostimulatory (*see* Example 5B) and can generate a MUC1-specific cytotoxic immune response in naïve immune cells (*see* Example 7).

The Examiner's argument that *Snijdewint's* report of PBMC proliferation in response *synthetic* MUC1 peptides equates to an immune response is specious. First, as already discussed, detecting pre-existing MUC1-reactive cells is at best a diagnostic tool, and is not a teaching or suggestion that an immune response was generated. Secondly, synthetic MUC1 peptides are not MUC1 molecules obtained from a cell line that expresses and/or secretes tumor associated MUC1 (or its lysate) as required by the claims. These synthetic peptides have different properties from MUC1 molecules isolated from cells or their lysates, such as size and glycosylation state.

In short, *Snijdewint* fails to teach or suggest a method of producing or identifying MUC1 molecules able to generate an immune response in humans from cells or their lysates and would even dissuade the skilled artisan from doing so in view of *Snijdewint's* report that MUC1 did not stimulate the proliferation of PBMCs from healthy donors and further in view of the MUC1's *immunosuppressive* effect on PBMCs treated with *C. albicans* extract. None of the remaining references alter these teachings. In fact *Ryuko* provides further evidence that *Snijdewint's* methods would not lead the skilled artisan to Applicants' methods, let alone with the requisite reasonable expectation of success. M.P.E.P. § 2143.02.

The antibody used in *Snijdewint* does not have the features recited in the claims, as evidenced by *Ryuko*

The Examiner relies on *Ryuko* to allege that the 139H2 antibody used in *Snijdewint* is an obvious variant of the A76-A/C7 antibody because they allegedly share

some binding properties. Office Action at 10. The Examiner concludes that it would be obvious to exchange these antibodies with predictable results. *Id.* Applicants disagree.

Applicants' claims require using an antibody that, *inter alia*, binds "a MUC1 fragment ...[where the binding] is made possible or increased by glycosylation of the threonine of a PDTR sequence." *Ryuko* provides evidence that, unlike the A76-A/C7 antibody, the 139H2 antibody used in *Snijdewint* lacks this feature. Specifically, the top panel of Figure 2 in *Ryuko* shows that the A76-A/C7 antibody effectively discriminates between a glycosylated MUC1 peptide (60-mer 3M GalNAc, which is glycosylated on the threonine of the PDTR repeat) and a non-glycosylated MUC1 peptide (60-mer). In contrast, the 139H2 antibody binds the glycosylated and non-glycosylated peptide with nearly identical reactivity and therefore does not distinguish between them. Thus, contrary to the Examiner's assertion, these antibodies are in no way "equivalent" or "interchangeable" and would not isolate identical MUC1 molecules. *Snijdewint* and *Ryuko*, alone or in combination, provide no teaching, suggestion, or motivation to substitute the 139H2 antibody used in the methods of *Snijdewint* with one that has the features recited in Applicants' claims. The remaining references do not change this.

Torabi-Pour Chu, and *Robertson* do not remedy the defects of *Snijdewint* and *Ryuko*, either alone or in combination

The Examiner cites *Torabi-Pour* for reporting a method of isolating a tumor antigen from a lysate of a tumor cell line. Office Action at 8. *Torabi-Pour* describes isolating antigens associated with MHC class molecules, not isolating the antigens *per se*. *See Torabi-Pour* at abstract. Importantly, *Torabi-Pour* does not discuss MUC1 in any context and therefore does not offer any suggestion to alter a method of obtaining

MUC1. Thus, *Torabi-Pour* doesn't remedy the underlying deficiencies of *Snijdewint* and *Ryuko*.

Chu was cited to evidence a method of isolating and formulating a tumor antigen in pharmaceutical composition. Office Action at 9. Like *Torabi-Pour,* however, *Chu* does not mention MUC1 in any context. Instead, *Chu* simply reports isolating an unrelated antigen (Ductal Carcinoma Antigen) and formulating it in saline. Accordingly, Chu offers no teaching or suggestion of how to isolate MUC1 that is able to generate an immune response.

Robertson was cited to allegedly describe providing a preparation comprising human MUC1 and that the preparation can be used to detect autoantibodies specific to MUC1. Office Action at 9. *Robertson* only describes isolating MUC1 from the pooled *sera* of patients, not a cell or its lysate. *See Robertson* at column 9, lines 50-63. *Robertson* then describes using this preparation as an antigen in an assay to detect auto-antibodies specific to MUC1, not to *generate* an immune response—its teachings are limited to diagnostics for detecting existing autoantibodies.

In short, *Ryuko*, *Torabi-Pour,* Chu, and *Robertson* do not remedy the defects of *Snijdewint*, since either alone or in combination they do not teach or suggest a method of producing or isolating a MUC1 molecule able to generate an immune response in humans with a reasonable expectation of success. *Snijdewint* does not suggest methods of producing immunostimulatory MUC1 nor does it use an antibody suited to such a purpose, as evidenced by *Ryuko*. None of *Torabi-Pour,* Chu, and *Robertson* change this. Thus, the collective disclosure of these references does not render Applicants' claims obvious and the rejection should be withdrawn.

CONCLUSION

Applicant respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 1, 2, and 9-11 in condition for allowance. Applicant submits that the proposed amendments of claims 1, 2, and 9 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner. Finally, Applicants submit that entry of this Amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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